Journal of Medical Bacteriology

Bacterial Agents and Antibiotic Resistance Profile in Pyelonephritis; A Comparison between Children with and without Urinary Tract Abnormalities in the North of Iran

Hadi Sorkhi [1], Niloofar Esmaeilzadeh [1], Mahmood Hajiahmadi [1], Peyman Hendizadeh [2], Abazar Pournajaf [3], Mohsen Mohammadi [1]*

1 Non-Communicable Pediatric Disease Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

2 Student Research Committee, Babol University of Medical Sciences, Babol, Iran.

3 Infectious Diseases and Tropical Medicine Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.

ARTICLE INFO

Article type:
Research Article

Article history:
Received: 11 Apr 2023
Revised: 09 Jul 2023
Accepted: 17 Aug 2023
Published: 01 Sep 2023

Keywords:
Antibiotic Resistance, Children, Pyelonephritis, Urinary Tract Abnormality.

ABSTRACT

Background: Pyelonephritis in children is a serious condition that is commonly encountered in clinical practice. Urinary tract abnormalities increase the risk of urinary tract infections (UTIs) and consequently antibiotic resistance. Our study aimed to evaluate the local trend in terms of bacterial uropathogen resistance in Babol, Iran, in children with pyelonephritis considering urinary tract abnormalities.

Methods: We recruited pediatric cases aged 1 month to 18 years who were admitted to Amirkola hospital with a diagnosis of pyelonephritis from 2016 to 2019. Children with negative urine cultures or incomplete imaging were excluded from the study. Causative agents were identified based on biochemical features. Antimicrobial in vitro resistance tests were performed using the disk diffusion agar test.

Results: A total of 105 children were included in the study. *E. coli* was the most common causative agent found in 93 (88.6%) patients. Most of the bacterial isolates were sensitive to amikacin and imipenem, and only 12.4% and 13.3% of isolates were resistant to this antibiotic. On the other hand, nalidixic acid represented the least effective treatment, with a resistance rate of 88.6%. A statistically significant difference was observed in resistance to nitrofurantoin and nalidixic acid between children with and without anomalies ($p < 0.05$).

Conclusion: High antibiotic resistance, especially in children with urinary tract anomalies, was identified for frequently used antibiotics. Our findings provide important implications regarding local patterns of uropathogens and antibiotic resistance in children with pyelonephritis.

- ***Please cite this paper as:*** Sorkhi H, Esmaeilzadeh N, Hajiahmadi M, Hendizadeh MP Pournajaf A, Mohammadi M. Bacterial Agents and Antibiotic Resistance Profile in Pyelonephritis; A Comparison between Children with and without Urinary Tract Abnormalities in the North of Iran. *J Med Bacteriol.* 2023; **11** (3, 4): pp.18-24.

*Corresponding Authors: Mohsen Mohammadi, Non-Communicable Pediatric Disease Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran.
Tel: +98-11-32354951, *E-mail:* dr.mohamadi61@yahoo.com

Introduction

Urinary tract infections (UTIs) represent the most common bacterial infection and a major cause of hospitalization in children (1, 2). Symptoms of UTI range from no symptoms to significant complications which can cause long-term morbidity (3). One type of UTIs is bladder infection termed cystitis. If cystitis is not cleared, the infection ascends to the kidneys causing pyelonephritis (4). Acute pyelonephritis (AP), also called febrile urinary tract infection, is considered one of the most serious bacterial illnesses in childhood (5-7). AP is generally associated with systematic signs of inflammation and can lead to renal scarring. Patients with AP generally present symptoms of feeding difficulty, fever, vomiting, and failure to thrive (8, 9). The diagnosis is based on the clinical presentation and urine analysis (10). The most common cause of AP is *Escherichia coli* (*E. coli*), with a prevalence of 80-90% (11-13). The remaining 10-20% causative pathogens include *Klebsiella*, *Enterococcus*, *Proteus*, and *Pseudomonas* species (14). Host condition and urinary tract abnormalities such as vesicoureteral reflux (VUR) and obstruction can play an important role in the progression of infection and renal scarring (15). Antibiotic therapy is served as the first choice of AP treatment and prevents the development of the condition (16-18). The choice of antibiotics should be guided by the knowledge of local resistance patterns, which significantly differ between different countries and also hospitals. Some uropathogens can produce Extended Spectrum β-Lactamase (ESBL), which mediates resistance to many antibiotics, including cephalosporin, the most preferred drugs for pyelonephritis treatment (1). This has decreased the number of available drugs for AP treatment and resulted in treatment failure and elongated hospital stay (19). Also, the choice of therapy is affected by urinary tract anomalies (20-22). There are a few data of differences in antibiotic choices in children diagnosed with pyelonephritis with and whitout urinary tract abnormalities in Iran. Therefore, this study aims to investigate causative uropathogens, antibiotic susceptibility, and resistance patterns in hospitalized children with pyelonephritis and compare these data between patients with or without urinary tract abnormalities.

Materials and Methods

Patient's selection

A cross-sectional study was designed in Babol, Iran. For this study, we recruited pediatric cases aged 1 month to 18 years who were admitted to Amirkola hospital with a diagnosis of pyelonephritis from 2016 to 2019. Children with incomplete imaging examinations were excluded. Laboratory results, demographic information, and urinary tract anomalies were gathered from the patient's medical records. Signed informed consent was obtained from all patients' parents or guardians.

Para-clinical findings

Ultrasonography of the urinary tract system was performed in all children. Lower urinary tract evaluation was done by radionuclide cystography (RNC) or voiding cystourethrography (VCUG). RNC was performed in girls if ultrasonography does not show bladder abnormality. VCUG was done in all boys as well as in girls with bladder abnormality on ultrasonography and also function disorders such as enuresis or daytime wetting. If RNC or VCUG were normal, DTPA (Diethylenetriamine pentaacetate) or IVP (Intravenous Pyelography) were employed for children with hydronephrosis to detect hydronephrosis's cause. Clean-catch midstream urine (CCU) samples were collected from children if they were toilet trained, and if not, catheters were used for collecting urine samples. Eligible patients were those with positive urine culture defined as growth $\geq 10^5$ CFU/mL of a single type of pathogenic organism with CCU or $\geq 10^4$ CFU/mL with catheter urine. Also, patients with symptoms of fever, urinary incontinence, urinary frequency, flank pain, and abdominal pain who had pyuria (>5

white blood cells [WBC]/HPF on urinalysis) are also included. Bacterial pathogens were identified according to biochemical features. Antimicrobial in vitro susceptibility tests were performed by the disk diffusion agar test for ampicillin (AMP; 20 µg), trimethoprim-sulphamethoxazole(SXT; 5 µg), cephalexin(LEX; 30 µg), ceftriaxone(FOX; 30 µg), cefotaxime(CTX; 30 µg), cefixime(CFM; 10 µg), gentamycin(GM; 10 µg), amikacin(AN; 30 µg), imipenem(IPM; 10 µg), amoxicillin-clavulanic acid(AMC; 10 µg), nitrofurantoin(NIT; 300 µg), and nalidixic acid(NA; 30 µg) (Padtan Teb Co, Iran).

Statistical data analysis

Statistical analysis was carried out using SPSS for Windows 18.0 (SPSS Inc., Chicago, IL, USA.). Continuous variables were presented as mean and standard deviation, and categorical variables were described as numbers and percentages. P value less than 0.05 was considered significant.

Result

During a five years period, 140 children were admitted to Amirkola hospital with the diagnosis of pyelonephritis, among which 35 cases were excluded due to negative urine culture. The remaining 105 children include 89 (84.8%) girls and 16 (15.2%) boys with a mean age of 15.84±10.11 months (range 1 month to 120 months).

A total of 64 (60.9%) children had at least one abnormality in their urinary tract system. VUR represented the most prevalent and constituted more than 80% of abnormalities. Other abnormalities include Ureteropelvic Junction (UPJ) Obstruction, Ureterovesical Junction Obstruction (UVJ), and Posterior urethral valves (PUV).

The most common causative agent was *E. coli*. It was isolated from the urine of 88.6% (n; 93) patients. Other organisms isolated include *Enterobacter* spp. (n; 6, 5.7%), *Pseudomonas* spp. (n; 4, 3.8%), and *Klebsiella* spp. (n; 2, 1.9%). The differences between bacterial pathogens in patients with and without abnormality are shown in Table 1. There was no significant difference between pathogen type and sex.

More than 80 percent of the isolates were sensitive to AN and IPM. The highest and lowest resistance rates in *E. coli* bacteria were for NA (87.1%) and AN (11.8%), respectively. Antibiotic resistance rates of other bacterial pathogens isolated from children are depicted in Table 2.

There was a statistically significant difference between resistance to NIT and NA in children with and without urological abnormalities, but in other cases, no statistically significant difference was found (Table 3). Also, there was no significant difference between antibiotic resistance and gender.

Discussion

The reliability of antibiotic choice in children with pyelonephritis is still being debated, especially in different countries with dissimilar bacterial resistant patterns (23). Additionally, urinary tract abnormalities can affect patients' response to antibiotic therapy. In this study, out of 140 children with pyelonephritis, 35 (25%) were excluded because of negative urine cultures. Comparably, in a study by Prabhu et al. (24), among 249 cases with pyelonephritis, 35% had negative urine cultures. This could be due to the use of antibiotics before admission or possible alternative diagnosis. Eighty-nine (84.8%) children in our study were females. This data is consistent with the fact that the relative risk of pyelonephritis is higher in female than male cases (25). Similarly, in studies by Ghiro et al. (6) and Prabhu et al. (24), 64% and 85% of patients

Table 1. Bacterial pathogens isolated from children with and without urinary tract abnormalities.

Bacterial pathogens	N [(%)] with anomaly	N [(%)] Without anomaly	P-value
E. coli	56 (60.2)	37 (39.8)	0.76
Pseudomonas spp.	2 (50.0)	2 (50.0)	0.99
Enterobacter spp.	5 (83.3)	1 (16.7)	0.40
Klebsiella spp.	1 (50.0)	1 (50.0)	0.99

Table 2. Antibiotic resistance in different bacterial pathogens.

Antibiotics	N [(%)] of *E. coli*	N [(%)] of *Pseudomonas spp.*	N [(%)] of *Enterobacter spp.*	N [(%)] of *Klebsiella spp.*	Total (%)
AN	11 (11.8)	1 (25.0)	1 (16.7)	0 (0.0)	13 (12.4)
IPM	13 (14.0)	0 (0.0)	1 (16.7)	0 (0.0)	14 (13.3)
GM	37 (39.8)	1 (25.0)	4 (66.7)	0 (0.0)	42 (40.0)
CTX	38 (40.9)	2 (50.0)	4 (66.7)	2 (100)	46 (43.8)
CFM	50 (53.8)	2 (50.0)	3 (50.0)	2 (100)	57 (54.3)
FOX	57 (61.3)	0 (0.0)	5 (83.3)	1 (50.0)	63 (60.0)
AMC	57 (61.3)	3 (75.0)	6 (100)	2 (100)	68 (64.8)
NIT	69 (74.2)	4 (100)	6 (100)	2 (100)	81 (78.1)
LEX	71 (76.3)	4 (100)	6 (100)	2 (100)	83 (79.0)
AMP	74 (79.6)	3 (75.0)	5 (83.3)	2 (100)	84 (80.0)
SXT	77 (82.8)	2 (50.0)	3 (50.0)	2 (100)	84 (80.0)
NA	81 (87.1)	4 (100)	6 (100)	2 (100)	93 (88.6)

Table 3. Resistance profile in children with and without urinary tract abnormalities.

Antimicrobial agents	N (%) with anomaly	N (%) without anomaly	P-value
AN	7 (10.9)	6 (14.6)	0.76
IPM	10 (15.6)	4 (9.8)	0.55
GM	28 (43.8)	14 (34.1)	0.41
CTX	30 (46.9)	16 (39.0)	0.54
CFM	38 (59.4)	19 (46.3)	0.19
FOX	40 (62.5)	23 (56.1)	0.54
AMC	45 (70.3)	23 (56.1)	0.13
NIT	54 (84.4)	27 (65.9)	0.02
LEX	50 (78.1)	33 (80.5)	0.77

AMP	51 (79.7)	33 (80.5)	0.92
SXT	53 (82.8)	31 (75.6)	0.45
NA	61 (95.3)	32 (78.0)	0.007

Ampicillin (AMP; 20 µg), trimethoprim-sulphamethoxazole(SXT; 5 µg), cephalexin(LEX; 30 µg), ceftriaxone(FOX; 30 µg), cefotaxime(CTX; 30 µg), cefixime(CFM; 10 µg), gentamycin(GM; 10 µg), amikacin(AN; 30 µg), imipenem(IPM; 10 µg), amoxicillin-clavulanic acid(AMC; 10 µg), nitrofurantoin(NIT; 300 µg), and nalidixic acid(NA; 30 µg).

consist of female cases. Based on our results, the most prevalent bacterial pathogen was *E. coli*, isolated from 88.6% of patients. Other causative agents include *Enterobacter* spp. in 6 (5.7%), *Pseudomonas* spp. in 4 (3.8%), and *Klebsiella* spp. in 2 (1.9%) cases. Flor-De-Lima et al. (26) evaluated 581 children with AP from 1994 to 2012 in four time periods. Their results showed that *E. coli* remained the leading uropathogen (70-80%) during those years. Other bacteria isolated include *Klebsiella* spp., *Enterococcus* spp., *Proteus* spp., and *Pseudomonas* spp., the prevalence of each was less than 10%. However, there was a significant decrease in the prevalence of *Klebsiella* spp. and *Enterococcus* spp. during the period studied. Based on our results, the most effective antibiotics for pyelonephritis treatment include AN and IPM, with resistance rates of 12.4% and 13.3%, respectively. NA represented the least effective treatment, and 88.6% of isolates were resistant to this antibiotic. A study by Duicu et al. (27) highlighted that NIT, ceftriaxone, AN, and carbapenem may be used for the empirical treatment of febrile or complicated UTIs in children. In contrast to our study, NA and NIT showed less resistance in their study. In another study by Prabhu et al. (24), the resistance rates of gentamycin, ceftriaxone, and cephalexin were lower than 10% in patients with pyelonephritis. The higher resistance rate indicated in our study may be due to geographical variations and higher consumption of antibiotics in Iran which is three times more than the mean global rate (28).

In our study, a total of 64 (60.1%) children had at least one urinary tract abnormality, including VUR, UPJ, UVJ, Obstruction, and PUV. In a study by Duicu et al. (27), from 331 children with UTI, 140 (42.29%) had an urinary tract abnormality. In another study by Koçak et al. (29), from 142 children with UTI, 22 (15.5%) and 26 (18.3%) had USG abnormalities and VUR. In addition, Ghiro et al. (6) indicate that of 1330 children with AP, 430 (32%) had at least one urinary tract abnormality. The higher rate of urinary tract abnormalities in our study may be due to that our study group is from one hospital or the different nature of pyelonephritis compared to other UTIs. Children with urinary tract abnormalities are at increased risk of developing UTIs (20, 30). VUR alters the unidirectional flow of urine, while Pelvi-ureteric Junction Obstruction (PUGO) leads to stasis, both increasing the risk of multiplying bacterial pathogens (31). Therefore, analyzing bacterial pathogens and antibiotic resistance patterns in uropathogens causing UTIs in children with urinary tract abnormalities is necessary. According to our results, there was no significant difference between bacterial pathogens isolated from children with and without anomalies. In the case of antibiotic resistance, children with urinary tract anomalies showed more resistance to NIT and NA than children without urological anomalies. Comparably, in a study by Duico et al. (27), more than 50 percent of multi-drug resistance pathogens were isolated from children with urinary tract anomalies.

Conclusion

In conclusion, the main pathogen responsible for pyelonephritis was *E. coli*. In laboratory conditions, AN and IPM are proposed as antibiotics of choice for children with and without urinary tract abnormalities suffering from pyelonephritis. The rate of antibiotic resistance was higher in our local

population compared to other studies. Therefore, constant monitoring of antimicrobial resistance patterns to develop appropriate treatment strategies at the national level is required. The high frequency of urinary tract abnormalities in children with pyelonephritis should be considered by medical practitioners. This is the first study that investigates antibiotic resistance in children with pyelonephritis and its association with urinary tract abnormalities in Iran. Our results provide useful information for empiric antibiotic treatment of children with pyelonephritis.

Funding Information

The present project approved by research code: A-12-392-29 and ethical code IRZUMS.RE,1396.275.

Ethics approval and consent to participate

This cross-sectional study was approved by the Ethics Committee of the Babol university of medical sciences with the Ethical code number IR.MUBABOL.HRI.REC.1398.353.

Conflict of interest

The authors have declared no competing interests.

References

1. Megged O. Extended-spectrum β-lactamase-producing bacteria causing community-acquired urinary tract infections in children. *Pediatr Nephrol* 2014; **29**(9):1583-7.
2. Marcus N, Ashkenazi S, Samra Z, Cohen A, Livni G. Community-acquired enterococcal urinary tract infections in hospitalized children. *Pediatr nephrol* 2012; **27**(1):109-14.
3. Upadhyay J, Bolduc S, Braga L, Farhat W, Bägli DJ, McLORIE GA, et al. Impact of prenatal diagnosis on the morbidity associated with ureterocele management. *J Urol* 2002; **167**(6):2560-5.
4. Jodal U. The natural history of bacteriuria in childhood. *Infect Dis Clin North Am* 1987; **1**(4):713-30.
5. Downs SM. Technical report: urinary tract infections in febrile infants and young children. *Pediatrics* 1999; **103**(4):e54-e.
6. Ghiro L, Cracco A, Sartor M, et al. Retrospective study of children with acute pyelonephritis. *Nephron* 2002; **90**(1):8-15.
7. Wald E. Urinary tract infections in infants and children: a comprehensive overview. *Curr opin pediatr* 2004; **16**(1):85-8.
8. Yousefichaijan P, Rezagholizamenjany M, Rafiei F, et al. The relationship between blood biomarkers level and the prognosis of nephrotic syndrome in the children. *Int J Pediatr* 2016; **4**(9):3489-97.
9. Shaikh KJ, Osio VA, Leeflang MM, et al. Procalcitonin, C-reactive protein, and erythrocyte sedimentation rate for the diagnosis of acute pyelonephritis in children. *CDSR* 2020; **9**.
10. Morello W, La Scola C, Alberici I, et al. Acute pyelonephritis in children. *Pediatr Nephrol* 2016; **31**(8):1253-65.
11. Montini G, Toffolo A, Zucchetta P, et al. Antibiotic treatment for pyelonephritis in children: multicentre randomised controlled non-inferiority trial. *Bmj* 2007; **335**(7616):386.
12. Neuhaus TJ, Berger C, Buechner K, et al. Randomised trial of oral versus sequential intravenous/oral cephalosporins in children with pyelonephritis. *Euro J pediatr* 2008; **167**(9):1037-47.
13. Shaikh N, Craig JC, Rovers MM, et al. Identification of children and adolescents at risk for renal scarring after a first urinary tract infection: a meta-analysis with individual patient data. *JAMA pediatr* 2014; **168**(10):893-900.
14. Alberici I, Bayazit AK, Drozdz D, et al. Pathogens causing urinary tract infections in infants: a European overview by the ESCAPE study group. *Euro J pediatr* 2015; **174**(6):783-90.
15. Hewitt IK, Montini G. Pediatric febrile urinary

tract infections: the current state of play. *Ital J pediatr* 2011; **37**(1):1-3.
16. Rezagholi-Zamnjany M, Yousefichaijan P. An overview on peritoneal dialysis. *Ann Res Dial* 2016; **1**(1).
17. Strohmeier Y, Hodson EM, Willis NS, et al. Antibiotics for acute pyelonephritis in children. *CDSR* 2014;**7**.
18. Yousefichijan P, Dorreh F, Zamenjany MR. Bartter's syndrome type 5; a case report. *J Ren Inj Prev* 2017; **6**(4):244-6.
19. Tankhiwale SS, Jalgaonkar SV, Ahamad S, et al. Evaluation of extended spectrum beta lactamase in urinary isolates. *Indian J Med Res* 2004; **120**(6):553-6.
20. Stein R, Dogan HS, Hoebeke P, et al. Urinary tract infections in children: EAU/ESPU guidelines. *Eur Urol* 2015; **67**(3):546-58.
21. Mishra OP, Abhinay A, Prasad R. Urinary infections in children. *Indian J Pediatr* 2013; **80**(10):838-43.
22. White B. Diagnosis and treatment of urinary tract infections in children. *Am fam physician* 2011; **83**(4):409-15.
23. Shigemura K, Ishikawa K. AAUS guideline for acute uncomplicated pyelonephritis. *J Infect Chemother* 2022. **28**(8):1092-7.
24. Prabhu A, Taylor P, Konecny P, et al. Pyelonephritis: what are the present day causative organisms and antibiotic susceptibilities? *Nephrology* 2013; **18**(6):463-7.
25. Czaja CA, Scholes D, Hooton TM, et al. Population-based epidemiologic analysis of acute pyelonephritis. *Clin infect dis* 2007; **45**(3):273-80.
26. Flor-de-Lima F, Martins T, Teixeira A, et al. Etiological agents and antimicrobial susceptibility in hospitalized children with acute pyelonephritis. *Acta Méd Port* 2015; **28**(1):15-20.
27. Duicu C, Cozea I, Delean D, et al. Antibiotic resistance patterns of urinary tract pathogens in children from Central Romania. *Exp Ther Med* 2021; **22**(1):1-7.
28. Hosseinzadeh K, Azimian J. Iranians' self-report knowledge and practice about arbitrary use of antibiotics. *J Clin Diagn Res* 2017; **11**(8):FC06.
29. Koçak M, Büyükkaragöz B, Çelebi Tayfur A, et al. Causative pathogens and antibiotic resistance in children hospitalized for urinary tract infection. *Pediatr Int* 2016; **58**(6):467-71.
30. Alper BS, Curry SH. Urinary tract infection in children. *Am Fam Physician* 2005; **72**(12):2483-8.
31. Twaij M. Urinary tract infection in children: a review of its pathogenesis and risk factors. *J. R. Soc. Promot. Health* 2000; **120**(4):220-6.